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Letter to the Editor

Response to Craddock et al.

To the Editor:

We share the sense of caution of Craddock et al. [1996] about accepting a single major locus (SML) model of bipolar disorder as being proved, as we explicitly stated in our original paper [Spence et al., 1995]. And we continue to emphasize three points: 1) segregation analysis only identifies the most likely mode of inheritance, given the data, not the *number* of loci segregating, 2) the autosomal-dominant fit to our data does *not* include an estimate of the number of loci which could be responsible for the disease (i.e., possible genetic heterogeneity), and 3) our fit of an SML does *not* account for all of the variation in the sample, and other factors (environmental and/or genetic) must be operative (i.e., possibly oligogenic).

We agree that if K_{MZ} is that much bigger than K_{sib}, then probably more than one locus has to be involved, which is addressed by our point 3 above. In addition, we have some concern about the accuracy of the K_R's, in particular K_{sib} and even more particularly K_{MZ}. Studies with twins are subject to reporting bias, inaccurate determination of zygosity, and subjective determination of affected status. These points are discussed in detail in all of the quality reviews of twin data from which the estimates arise [e.g., see Hall, 1996].

Craddock et al. [1996] are, of course, also correct that segregation analysis can reveal only the best-fitting model *among* those models tested, so that is clearly a limitation of our analysis. On the other hand, we were able to allow for age and cohort effects which they did not undertake in their analysis. The analysis by Craddock et al. [1995] is also limited by the fact that they did not include polygenic inheritance as an alternative hypothesis.

However, the more fundamental point stressed by these investigators in their letter seems to be that if indeed multiple loci are involved in the inheritance of bipolar disorder, then affected sib-pair (ASP) methods would be more appropriate than lod score analyses for mapping the loci. We are much less convinced that this is so [Greenberg et al., 1996]. To apply the distinction made by Craddock et al. [1995], if inheritance is two-locus "oligogenic/multiplicative," then the work of Vie land et al. [1992, 1993] and of Goldin and Weeks [1993 shows that single-locus lod score analyses can ver closely approximate the power of full two-locus lo score analyses. If inheritance is "oligogenic/heter ogeneous," lod score methods have been developed t allow for heterogeneity, including statistical tests fo the proportion of linked families and the corrected es timate of recombination [e.g., see Hodge et al., 1983 The test by Faraway [1993] for linkage in the presenc of heterogeneity has been shown to be quite powerful i this situation. We agree that the power of the lod scor method can be reduced when the parameters of th trait model are misspecified, but given the very larg sample sizes required for ASP [e.g., see Risch, 1994 Vieland et al., 1992, 1993; Goldin and Weeks, 1993], w are not prepared to ignore lod score methods and focu solely on ASP methods. One can collect families appro priate for lod score methods and analyze them usin both parametric lod score tests and nonparametri tests that utilize information from the entire nuclea family, such as the Haseman-Elston (H-E) method o IBD sib-pair linkage [Haseman and Elston, 1972 Blackwelder and Elston, 1985]. This approach may b a reasonable compromise utilizing the strengths o both parametric and "nonparametric" methods in single study.

The whole discussion of lod scores vs. ASP may soo be moot. Knapp et al. [1994] have already demon strated that one ASP approach is statistically equiva lent to the assumptions of an autosomal-recessiv model lod score analysis. And very recently, Whitte more [1996] argued that the nonparametric method are simply subsets of the same likelihood as the para metric approaches. She interpreted this to mean tha "nonparametric" is a misnomer for the affected relativ pair test, stating, "Thus, contrary to common parlance this test is not model-free." If it turns out that nonpara metric ASP methods are simply less powerful subset of parametric methods, sharing the same model as sumptions, then there should be little to argue in favo of throwing away power.

Hopefully the genetic epidemiology and psychiatr communities will engage in an active dialogue on th merits of parametric (lod score) and nonparametri (APM, ASP, and H-E) analyses in order to better un derstand the true limitations of each. We are encour aging such a dialogue, but it bears more directly o identifying the actual locus (or loci) than on the inter pretation of our segregation analysis.

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